REMARKS

I. Status of the Claims

Claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 318-323, 325 and 326 were pending in the March 9, 2011 Office Action. Claims 318-323 were withdrawn and claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 were examined therein. With this Reply, claim 318 is amended. The amendment is made without prejudice or disclaimer.

II. Rejection under 35 U.S.C. § 103

Claims 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 are rejected under 35 U.S.C. 103(a) as being unpatentable over Izant (Chimeric Antisense RNAs, in Gene Regulation: Biology of Antisense RNA and DNA, pp. 183-195, 1992), Frankel et al. (U.S. 5,989,814) and Zieve et al. (Critical Rev. in Biochem. & Molec. Biol. Vol. 25, No. 1, pp. 1-46, 1990), the combination in view of Meador et al. (US 5,547,862), Dahlberg et al. (The Genes & Transcription of the Major Small Nuclear RNAs, in Structure and Function of Major & Minor Small Nuclear Ribonucleoprotein Particles, pp. 38-70, 1988), Calabretta et al. (US 5,734,039) and Binkley et al. (Nucleic Acids Research, 1995, 23:3198-3205), the combination in further view of Craig et al. (WO 95/08635) and Alul et al. (U.S. 5,532,130). Applicants respectfully request reconsideration and withdrawal of this rejection in light of the following comments.

Applicants first note that Frankel et al. is not prior art to the instant application, since the earliest priority date for that patent is its filing date, April 1, 1997, whereas the instant application is a divisional of Application No. 08/574,443, filed December 15, 1995.

With regard to claims 265, 268, 272, 284, 288-290, 296, Applicants note that none of the cited references that discuss snRNA, *i.e.*, Izant, Dahlberg et al., nor Zieve et al., teach or suggest a construct encoding an snRNA nuclear localization sequence, a

reimportation signal and an antisense nucleic acid sequence, where the antisense nucleic acid sequence replaces removed (*i.e.*, deleted) stem-loop sequences.

The Office Action asserts that Izant teaches the replacement of an snRNA stem-loop sequence with an antisense sequence. Applicants disagree. As described in the caption for FIG. 2 of Izant, "The diagram shows the mature *Xenopus* U2 transcript that was mutated to insert Xho sites that facilitated chimeric gene construction." With the addition of this insert of a restriction enzyme site linker sequences, a variety of fragments from the CAT gene were then inserted in a second insertion process. As such, this construct clearly does not correspond to the feature of claim 205 "wherein said antisense nucleic acid sequences replaces stem loop sequences removed from said U1, U2 or U4 snRNA...." The term "replace" would be understood by one skilled in the art that sequences were removed in order to substitute some other sequences. This understanding is even more clearly emphasized by the additional term "removed". In contrast to that claimed feature, Izant carries out sequential insertions of extra nucleotide sequences into the U2 sequence, first with a linker segment and then with various antisense sequences. As such, Applicants believe that the Office Action is incorrect in summarizing the Izant constructs as ""further comprising an antisense which replaces the stem-loop sequence removed from the U1, U2 or U4 snRNA." Applicants further assert that there is no description of a removal of a stem-loop sequence and a subsequent replacement step, as claimed, in Izant.

Applicants also note that the remainder of the references cited in this rejection, *i.e.*, Calabretta et al., Binkley et al., Craig et al., Meador et al. and Alul et al., also do not teach or suggest a construct comprising an antisense nucleic acid sequence that replaces removed or deleted snRNA stem-loop sequences, since none of those references are related to snRNA sequences, or the replacement of stem-loop sequences. As such, the combination of references do not teach or suggest each element of claims 265, 268, 272, 284, 288-290, 296 and therefore do not make those claims obvious.

With regard to claims 299, 303, 304, 308, 312, 313, 325 and 326, directed to

> An isolated multi-cassette nucleic acid construct comprising at least three copies of a promoter, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each promoter, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral RNAs in a cell or binds to a specific viral protein, wherein each specific nucleic acid so produced binds to different target nucleic acid sequences.

(claim 299) and similar constructs comprising more than one copy or an snRNA promoter or bacteriophage promoter (claim 325), or three copies of a promoter producing specific nucleic acids directed to HIV RNAs or proteins (claim 326), Applicants first note that Izant et al. do not teach or suggest a construct comprising at least three, or even two, copies of a promoter. Additionally, in any constructs described by Meador et al. that have multiple promoter copies, those promoters are <u>different</u> promoters, not three <u>copies</u> of a promoter, as claimed.

Calabretta et al. also do not describe a construct with <u>three</u> copies of a promoter. As discussed in the previous response and in the Office Action, Calabretta et al. only teach "a composition for introducing two different antisense oligonucleotides specific for two different genes in a cell." (Office Action at page 9). Indeed, Calabretta et al. is primarily concerned with administration of synthetic oligonucleotides. There is only a brief mention therein of a construct having a first promoter and a second promoter (see Col. 9, lines 14-30 of Calabretta et al.). Additionally, with respect to claim 325, Calabretta et al. do not discuss the use of an snRNA promoter or a bacteriophage promoter.

As discussed in the Office Action, neither Binkley et al., Craig et al., nor Alul et al. teach or suggest a construct having three copies of a promoter.

The Action combines the references by asserting "[i]t would have been obvious to design a multi-cassette nucleic acid construct comprising the U1, U2, or U4 snRNP transcriptional constructs taught previously by Izant and Zeist, and comprising the nuclear localization domain taught by Frankel for expression of viral inhibitory constructs, and relying on the teachings of multiple promoter constructs taught

previously by Meador because the elements required for producing such recombinant nucleic acids, including antisense and sense nucleic acids, using portions of the snRNAs as instantly claimed were well known in the art." Office Action at page 7. Applicants disagree, since none of the cited references teach or suggest using more than one **copy** of the **same** promoter in the construct, which is an element of each of the subject claims. Indeed, Binkley et al. and Craig et al. do not even discuss the use of any promoters. The skilled artisan would not have a motivation to use more than one copy of the same promoter since the cited references all teach that use of different promoters, when more than one promoter is discussed, is completely effective for the methods described therein. Thus, the very concept of using more than one copy of the same promoter is not introduced by any of the cited references, and none of the cited references provide any motivation for using more than one copy of a particular promoter, rather than the universally taught different promoters in widespread use at the time of filing. Applicants thus assert that the combination of references do not teach or suggest at least the claim element of multiple copies of a single promoter, and provide no motivation for using such a construct. Therefore, the combination of references do not make the instant claims obvious. Withdrawal of this rejection is thus respectfully requested.

III. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of all rejections and examination of withdrawn claims 318-323, since those withdrawn claims include all of the limitations of the examined claims.

The United States Patent and Trademark Office is hereby authorized to charge the extension of time, as well as any other fees required to maintain pendency of this application, to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,

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